REMARKS

Amendments to the Claims

Claims 116, 177-182 and 243-303 are pending. Claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 stand rejected. Claims 177-179, 181-182, 243, 251-252, 261, 280, 289, 292, 295, 299 and 301 stand withdrawn. With this response, Applicant cancels claim 298 and amends claims 116, 254, 256-29, 262, 277 and 284-286. No new matter has been added.

Election of Species

Applicant respectfully disagrees with the Examiner's arguments regarding the request for an election of species and reserves the right to address these arguments in a Petition.

Priority

Applicant respectfully disagrees with the Examiner's arguments regarding the priority date of the pending claims and reserves the right to address these arguments if and when the priority date becomes material to the patentability of the pending claims.

Claim Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 under 35 U.S.C.§ 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In particular, the Examiner states that claims 116, 256, 257, 277 and 285 are unclear in what is encompassed by the term "substantially complementary" (See page 7 of the Office Action). The Examiner states that:

> "Although one of ordinary skill in the art would reasonably interpret how the term "substantially complementary" is applied to the comparison of two sequences, such as

two stem sequences, in light of the definition provided in the instant specification stating: "Two sequences are considered 'substantially complementary' herein if their complementarity is at least 50%", the term 'substantially complementary' is unclear in Claims 116, 256, 257, 277 and 285, as written, as applied to embodiments encompassing portions of sequences which read on single and/or dinucleotide sequences. Therefore, one of ordinary skill in the art would not be able to determine what is encompassed by the term "substantially complementary" with regards to a single base-pair interaction and the metes and bounds of Applicants invention can not be determined."

Solely in order to expedite prosecution, Applicant amends claim 116 to recite complementarity or substantial complementarity between portions of "at least 6 nucleotides in length." Support for this amendment can be found, for example, in paragraph [0062] of the published application. Applicant amends claims 256 and 257 (aswell as claims 254 and 284) to recite complementarity between portions of "at least 4 nucleotides in length." Support for this amendment can be found, for example, in paragraph [0077] of the published application. Applicant amends claims 277 and 285 so that the terms "substantially complementary" are no longer present. Applicant submits that, as amended, claims 116, 256, 257, 277 and 285 (aswell as claims 254 and 284), and claims dependent therefrom, are not indefinite.

The Examiner has rejected claim 254, which recites the limitation "the engineered nucleic acid molecule," as allegedly lacking sufficient antecedent basis. This limitation has been removed from claim 254. Applicant respectfully submits that, as amended, claim 254, and claims dependent therefrom, do not lack antecedent basis.

The Examiner has rejected claim 259, which recites the limitation "the sequence of the non-stem-forming portion of the first nucleic acid molecule," as allegedly lacking sufficient antecedent basis. As amended, claim 259 recites "the non-stem forming portion." Applicant respectfully submits that, as amended, claim 259 does not lack antecedent basis. A similar amendment has been made to claim 258.

Applicant therefore respectfully requests that the Examiner reconsider and withdraw the rejection of claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 under 35 U.S.C.§ 112, second paragraph.

Claim Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

According to the USPTO's Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, first paragraph, "Written Description" Requirement ("the Guidelines"): "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." MPEP § 2163(I). The Guidelines further state that "possession may be shown in many ways." For example, "[a]n applicant may show that the applicant was in possession of the claimed invention by disclosure of detailed, relevant identifying characteristics, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." MPEP § 2163(II)(A)(3)(a).

In the Office Action, the Examiner rejects the claims for lack of written description, and concludes by stating the following:

> "[…] the instant claims require a correlation between the functional requirement of 'forming a stem-loop structure' and 'acting to repress translation' (i.e. the crR molecules) or to 'derepress translation' (i.e. the taR molecules) and the structural requirement of a nucleic acid sequence.
>
> […] Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification [...] Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description of the taR 12 and crR 12 nucleic acid molecules corresponding to SEQ ID NO'S 55 and 56, respectively, and to the nucleic acid molecules identified in the examples by SEQ ID NO, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims."

Applicant respectfully traverses this rejection and submits that the written description requirement is satisfied in this case. In particular, as discussed below, the subject application provides ample guidance regarding correlations between the function and structure of the claimed systems, such that one of ordinary skill in the art would recognize that the Applicant was in possession of systems encompassed by the claims.

The subject application teaches nucleic acid based systems that enable post-translational regulation of gene expression. At the RNA level these systems involve pairs of cognate RNA molecules: a cis-repressive RNA molecule (crRNA) and a trans-activating RNA molecule (taRNA). The first of these nucleic acid molecules represses translation of an open reading frame (ORF) while the second interacts with the first nucleic acid molecule in a way that derepresses and thereby activates translation of the ORF. For purposes of illustration, the following paragraphs explain how the *structure* of an exemplary prokaryotic system from the specification correlates with these repression / activation *functions*. As will become apparent from this illustration, because these functions result from structural considerations that are driven by well understood and predictable rules (e.g., Watson-Crick pairing), a person of ordinary skill in the art would immediately recognize that these structure / function correlations are generalizable to other systems. This is particularly so when one also considers the extensive guidance that Applicant provides in the specification regarding the design of crRNA structures (see paragraphs [0068]-[0099] and [0157]-[0179] of the published application[1]), the design of cognate taRNA structures (see paragraphs [0100]-[0115] and [0180]-[0187]), and methods for selecting cognate pairs using simple *in vitro* assays (see paragraphs [0123]-[0128] and [0188]-[0201]).

Since the written description requirement needs to be assessed in light of the system as claimed we begin by turning to claim 116, as amended, which reads as follows:

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[1] All references to paragraphs are made in reference to paragraphs in US Publication No. 2007/0136827.

A **system** for control of gene expression comprising:

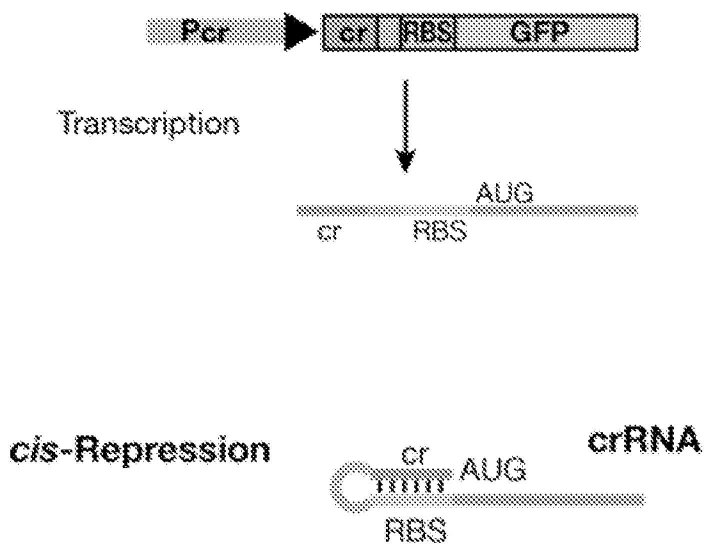
(i) an isolated **first nucleic acid molecule** comprising a cis-repressive sequence element upstream of an open reading frame (ORF), or including part of the open reading frame, wherein the cis-repressive sequence element forms part of a stem-loop structure that represses translation of the ORF; and

(ii) an isolated **second nucleic acid molecule** comprising first and second stem-forming portions and a non-stem-forming portion, wherein the non-stem-forming portion connects the 3' end of the first stem-forming portion and the 5' end of the second stem-forming portion to form a loop, and wherein a portion of at least 6 nucleotides in length of the first or second stem-forming portion of the second nucleic acid molecule is complementary or substantially complementary to a portion of at least 6 nucleotides in length of the first nucleic acid molecule and interacts with the first nucleic acid molecule to disrupt the stem-loop structure in which the cis-repressive sequence element participates and thereby derepress translation of the ORF.

Below, we discuss the structure, function and structure / function correlation of the first and second nucleic acid molecules in turn.

First Nucleic Acid Molecule (cis-repressor)

A system for control of gene expression comprising an isolated first nucleic acid molecule comprising a cis-repressive sequence element upstream of an open reading frame (ORF), or including part of the open reading frame, wherein the cis-repressive sequence element forms part of a stem-loop structure that represses translation of the ORF;



As shown above for an exemplary first nucleic acid molecule, a cis-repressive sequence is strategically introduced upstream of an open reading frame (ORF) of a target gene (e.g., GFP, shown above) or including part of the ORF. The cis-repressive sequence is designed to permit the formation of a stem-loop structure that represses translation of the ORF. As shown above for an exemplary prokaryotic system, the cis-repressive sequence may hybridize through complementary base pairing with the Ribosome Binding Site (RBS) to form the stem while a short intervening sequence forms the loop. In the above example, the stem loop structure that is

formed by the cis-repressive sequence sequesters the RBS, thereby preventing ribosome docking and translation initiation. In general however, and as described in the specification, the cis-repressive sequence may be complementary or substantially complementary to any portion of the sequence between the 3' end of the cis-repressive sequence and the 5' end of the ORF (see paragraph [0081]). The stem loop structure may even include a portion of the 5' region of the ORF (see paragraph [0079]). When there is no RBS (e.g., in a eukaryotic system), the cis-repressive sequence may be designed to form a stem-loop structure within the 5' UTR, between the IRES[2] and the 5' end of the ORF and/or encompassing all or part of a Kozak consensus sequence (see paragraph [0079]). In each case, the same correlation links the structure (i.e., sequence) and function (i.e., repressing translation of the ORF) of the first nucleic acid molecule, namely: hybridization of the cis-repressive sequence leads to the formation of a double-stranded stem-loop (hairpin) structure that prevents the ribosome from gaining access to the appropriate location on the mRNA from which to initiate translation from the downstream start codon (see paragraph [0075]).

In general, the sequence (i.e., structure) of putative cis-repressive sequences can be computationally predicted and assembled in solution by generating an initial set of sequences that render the desired stem-loop structure upon folding by Watson-Crick pairing (e.g., with the RBS). In general, optimal cis-repressive sequences will produce a partially unstable stem-loop structure that can be disrupted by a cognate trans-activating sequence (the second nucleic acid molecule which is discussed below). The relative stability of different stem-loop structures can be predicted from ΔG values that can be readily calculated using a variety of computer programs known in the art (see paragraph [0085] and [0108], e.g., the inventors used the Mfold™ program but other programs such as RNAfold™ could also be used). The specification describes how appropriate ΔG values can be predictably obtained in order to achieve desired levels of hybridization stringency, e.g., by introducing dispersed mismatches and/or inner loops into the sequence (see, for example, paragraphs [0084] and [0105]). It is also worth noting that the settings of computer programs such as Mfold can be adjusted to predict structures and ΔG values

[2] Internal Ribosome Entry Site.

under different experimental conditions (e.g., temperature, pH, ionic strength, etc.). Filters can also be applied to exclude putative cis-repressive sequences that would produce more than one predicted secondary structure (see paragraph [0174]). As a result, cis-repressive sequences can be designed that produce predictable structures under the desired experimental conditions.

From the foregoing it should be readily apparent that the subject application describes a clear correlation between the claimed stem-loop structure of the first nucleic acid molecule and its function of repressing translation of the ORF. Under the Guidelines, this description of a structure function correlation is sufficient to satisfy the written description requirement.

We now turn our attention to the second (cognate) nucleic acid molecule and explain how its structural features correlate with the claimed derepression (activation) function.

Second Nucleic Acid Molecule (trans-activator)

> *an isolated second nucleic acid molecule comprising first and second stem-forming portions and a non-stem-forming portion, wherein the non-stem-forming portion connects the 3' end of the first stem-forming portion and the 5' end of the second stem-forming portion to form a loop, and wherein a portion of at least 6 nucleotides in length of the first or second stem-forming portion of the second nucleic acid molecule is complementary or substantially complementary to a portion of at least 6 nucleotides in length of the first nucleic acid molecule and interacts with the first nucleic acid molecule to disrupt the stem-loop structure in which the cis-repressive sequence element participates and thereby derepress translation of the ORF*
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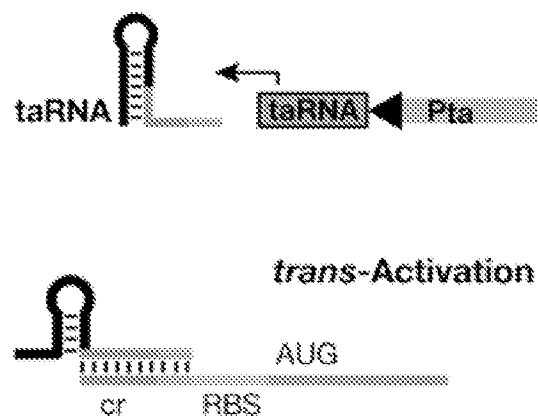
> 
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As shown above at the RNA level, the second nucleic acid molecule is a small, non-coding trans-activator (taRNA) that targets the first cis-repressive nucleic acid molecule with high specificity. As described in the specification and as shown above, Watson-Crick base pairing interactions between the first and second nucleic acid molecules permit conformational changes so that a duplex structure forms between the two molecules. In the example above, the

duplex structure "disrupts the stem-loop in which the cis-repressive sequence participated, thereby making the region upstream of the ORF accessible to the ribosome. [T]he ribosome can now gain entry to the RBS and translation can proceed" (see paragraph [0104]). In general however, and as described in the specification, the trans-activator sequence may be complementary or substantially complementary to any portion of the first nucleic acid molecule that will result in disruption of the stem-loop structure involving the cis-repressive sequence element (including the stem or loop portions of the cis-repressive sequence, see, for example paragraphs [0101]-[0102]). In each case, the same correlation links the structure (i.e., sequence) and function (i.e., derepressing translation of the ORF) of the second nucleic acid molecule, namely: hybridization of a portion of the second nucleic acid molecule to a portion of the first nucleic acid molecule leads to the formation of a duplex structure that disrupts the stem-loop structure in which the cis-repressive sequence element participated and thereby makes the region upstream of the ORF accessible to the ribosome (see, for example, paragraph [0104]).

As claimed and described above, the second nucleic acid molecule includes a stem-loop structure. This stem-loop structure is included in order to sequester a portion of the second nucleic acid molecule that is complementary or substantially complementary to the first nucleic acid molecule (e.g., a portion of an RBS-like sequence in the illustration above). As discussed in the specification, this reduces the likelihood that free second nucleic acid molecules will bind ribosomes (see paragraph [0174]). As outlined above for the cis-repressive sequence, in general, the structure (i.e., sequence) of the second nucleic acid molecule can be computationally predicted and assembled in solution by generating an initial set of sequences that produce the desired stem-loop structure upon folding by Watson-Crick pairing. As described above for cis-repressive sequences, computer programs (e.g., Mfold™, RNAfold™, etc.) can be utilized to predict the secondary structure of the nucleic acid sequences. Generally, optimal sequences are selected from the initial set with the sequence of a cognate cis-repressive sequence in mind. Additionally, the stability of the secondary structure of any given second nucleic acid molecule can be determined (e.g., by ΔG value calculations under the desired conditions) and compared with the stability of the duplex formed between the first and second nucleic acid molecules.

Secondary nucleic acid molecules that are more stable when duplexed with the first nucleic acid molecule are suitable for use in a claimed system. As described above, in order to achieve an appropriate ΔG value for desired levels of hybridization stringency, dispersed mismatches and/or inner loops may be introduced into the sequence of the second nucleic acid molecule (see, for example, paragraphs [0084] and [0105]).

From the foregoing it should be readily apparent that the subject application describes a clear correlation between the structural features of the second nucleic acid molecule along with the associated structural changes that result from its hybridization to the first nucleic acid molecule and its function of derepressing translation of the ORF. Under the Guidelines, this description of a structure function correlation is sufficient to satisfy the written description requirement.

Conclusion

Under the Guidelines, the written description requirement is met for the system of claim 116 and its dependent claims if the subject application discloses a correlation between the function of repressing or de-repressing translation and the claimed structures of the first and second nucleic acid molecules, respectively.

As set forth in the specification and outlined above, the subject application discloses and claims the structural features that are responsible for the claimed functions. Thus the first nucleic acid molecule includes a cis-repressive sequence element that forms part of a stem-loop structure that prevents the ribosome from gaining access to the appropriate location on the mRNA from which to initiate translation from the downstream start codon (e.g., the RBS in our illustration). A portion of the second nucleic acid molecule is complementary or substantially complementary to a portion of the first nucleic acid molecule and interacts with the first nucleic acid molecule to disrupt the stem-loop structure in which the cis-repressive sequence element participated and thereby derepress translation of the ORF.

Crucially, the correlations between the structural features and claimed functions of both nucleic acid molecules are governed by the fundamental rules of Watson-Crick base pairing that are well understood in the art. In fact, they are so well understood that the structures and stabilities of the first and second nucleic acid molecules can be *computationally predicted* using tools that are available in the art. These same tools can also be used to predict whether the cognate pairs will favor the type of duplex formation that will lead to depression of ORF translation.

In addition to providing generally applicable teachings based on well understood correlations between structure and function, the subject application also described how these teachings were actually used by the inventors to generate and test several cognate pairs of nucleic acid molecules, e.g., crR12 and taR12, crR10 and taR10, among others (see Examples 1-5).

The Examiner states that "the specification only uses computer programs such as Mfold to predict the secondary structures that could possibly form for any given nucleic acid sequence but the actual secondary structure and nucleic acid interactions under various in vitro or in vivo conditions is unpredictable without experimentation such as secondary structure studies and compensatory mutation analysis to verify stem-loop structures predicted by computer programs" (see page 12 of the Office Action). As a result, the Examiner seems to take the position that Applicant was only in possession of the specific cognate pairs that were reduced to practice.

Applicant respectfully submits that in the context of the claimed systems and in view of the disclosed correlations, the Examiner's emphasis on highly stringent systems and disclosure of specific sequences is inappropriate. The fact that all computationally predicted systems might not work *in vitro* or *in vivo* without further experimentation does not mean that Applicant was only in possession of systems that were actually reduced to practice. Applying such a high standard would raise the standard for satisfying the written description requirement to reduction to practice which is clearly not the law (e.g., see the Guidelines which explicitly state that the written description requirement can be satisfied by sufficient disclosure of functional characteristics when coupled with a known or disclosed correlation between function and

structure). Besides, the skilled person would appreciate that in addition to the computational tools described above, interactions between cognate pairs of nucleic acid molecules could also be *routinely* evaluated by methods that were well known in the art and described in the subject application (see, for example, paragraphs [0123]-[0128]). Now that Applicant has described the structural features that are required to produce cognate pairs, the skilled person would immediately recognize that Applicant could have generated additional cognate pairs through routine experimentation, i.e., that Applicant was "in possession" of the claimed invention. The fact that Applicant did not laboriously generate hundreds of additional cognate pairs using these methods would not, in the eyes of the skilled person, suggest that Applicant was any less "in possession" of the claimed invention. Applicant also wishes to point out that, one skilled in the art would recognize that the subject application provides guidance for designing and using cognate pairs that can be tailored to different situations and the needs of the practitioner. For example, as described in the specification, not all cognate pairs that are encompassed by the present disclosure need to be capable of stringent repression. In fact, in certain situations the teachings may be used to create cognate pairs that allow for less stringent repression (e.g., designing a "knock-down" rather than a "knock-out" system as discussed in paragraph [0077]).

In view of the foregoing Applicant respectfully requests that the Examiner withdraw this rejection.

Claim Rejection under 35 U.S.C § 101

The Examiner has rejected claim 116 under 35 U.S.C. § 101 as allegedly being directed to non-statutory subject matter (see page 14 of the Office Action). Specifically, the Examiner states:

> "Claim 116 does not sufficiently distinguish over systems comprising a first and second nucleic acid as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. For example, Altuvia et al. […] report that both bacterial and mammalian cells represent naturally occurring systems comprising (i) first stem-loop RNAs comprising cis-repressive sequence elements located upstream and/or including part of an ORF that repress translation of the ORF; and (ii) second stem-loop RNAs that are complementary to a portion of the first stem-loop RNAs that interact with the first stem-loop RNAs to derepress translation of the ORF…"

Solely in order to expedite prosecution, Applicant amends claim 116 to recite an "isolated" first and second nucleic acid molecule as suggested by the Examiner. Applicant therefore respectfully requests that the Examiner withdraw this rejection.

Claim Rejection under 35 U.S.C. § 102

Rejection over Argaman et al.

The Examiner has rejected claims 116, 244-246, 250, 253-260, 262-279, 281-282, 286-288, 290-291, 293-294, 297-298, and 303 under 35 U.S.C. § 102(b) as being anticipated by Argaman *et al.* (*J. Mol. Biol.* 2000; 300:1101). Specifically, the Examiner states:

> "Argaman *et al.* teach a system for control of gene expression comprising: (i) a first RNA molecule comprising a cis-repressive RNA sequence element, at least a portion of which is complementary or substantially complementary to a ribosome binding site (RBS), and which is located upstream of and including part of an open reading frame (ORF), wherein the first RNA molecule forms a stem-loop structure that represses translation of the ORF; and (ii) a second RNA molecule, called OxyS RNA, comprising

first and second stem forming portions and a non-stem-forming portion, wherein the non-stem-forming portion connects the 3' end of the first stem-forming portion and the 5' end of the second stem forming portion to form a loop, and wherein a portion of the second RNA molecule is complementary or substantially complementary to a portion of the first RNA molecule and interacts with the first RNA molecule ***to derepress translation of the ORF*** (e.g. see especially Table 1, page 1105). Table 1 (page 1105) shows measuring the level of translation by the B-Galactosidase activity assay using a system comprising a first RNA molecule (the fhlA32-lacZ fusion RNA) and a second RNA molecule (the OxyS RNA)…" [Emphasis added]

Applicant respectfully traverses this rejection and submits that Argaman *et al.* does not anticipate the claimed invention. Argaman *et al*. describes a natural system in *E. coli* for regulation of gene expression where OxyS is a small untranslated RNA that is induced in response to oxidative stress. OxyS acts in *trans* to *inhibit translation* of two target genes, rpoS and fhlA. Argaman *et al*. "focus on the *repression* by OxyS," finding that "kissing complex formation between OxyS and fhlA at two sites results in a stable antisense-target complex" (see paragraph spanning pages 1101-1102). Table 1 (see page 1105) depicts the *repression levels* of OxyS on various fusion constructs containing the fhlA gene or mutations thereof. Contrary to the Examiner's statement, Table 1 does not show that, without adding OxyS RNA, the translation of the fhlA fusion is repressed in *cis*. Rather, Table 1 shows that in the absence of OxyS (column labeled pKK177-3), translation occurs, as measured by β-galactosidase activity. When OxyS is added (column labeled poxyS), translation is repressed, as measured by a decrease in β-galactosidase activity. More specifically, Table 1A shows that OxyS represses translation of a both wild-type and mutant fhlA fusions, although at varying levels. Table 1B shows that compensatory mutations in OxyS restore or increase repression of the wild-type and mutant fhlA fusions.

Applicant submits that Argaman *et al.* does not teach a system in which a first RNA molecule acts to repress in *cis* and a second RNA molecule interacts in *trans* with the first RNA molecule *to de-repress translation of the ORF* as claimed. Accordingly, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Rejection over Altuvia et al.

The Examiner has rejected claims 116, 180, 244-245, 250 and 275 under 35 U.S.C. § 102(b) as being anticipated by Altuvia *et al.* (*EMBO* 1998; 17(20):6069). Specifically, the Examiner states:

> "Regarding base Claim 116 and dependent Claim 250, Altuvia *et al.* teach that both bacterial and mammalian cells represent naturally occurring systems comprising (i) first stem-loop RNAs comprising cis-repressive sequence elements located upstream and/or including part of an ORF that repress translation of the ORF; and (ii) second stem-loop RNAs that are complementary to a portion of the first stem-loop RNAs that interact with the first stem-loop RNAs ***to derepress translation of the ORF*** (e.g. page 6069, paragraphs 1-2). Altuvia et al. teach the first RNA in the form of the native fhlA mRNA or in the form of their recombinant fhlA32-lacZ fusion construct. Regarding base Claim 180, Altuvia et al. teach cell systems comprising truncated OxyS RNA transcripts in combination with fhlA-lacZ fusion transcripts and the (e.g. page 6069, paragraph 4, lines 9-11) and also comprising the X-Gal inducer (e.g. page 6073, paragraph 6, lines 1-5), which reads on a kit, comprising an oligonucleotide comprising "a crRNA sequence", or "*a taRNA sequence*" or both, and also comprising an inducer." [Emphasis added]

Applicant respectfully traverses this rejection and submits that Altuvia *et al.* does not anticipate the claimed invention. Similar to Argaman *et al.* described above, Altuvia *et al*. describes a natural system in *E. coli* that regulates gene expression, involving OxyS, which is a small untranslated RNA that is induced in response to oxidative stress. As described above, OxyS acts in *trans* to *inhibit translation* of two target genes, rpoS and fhlA. Specifically, Altuvia *et al.* teaches that "both fhlA and rpoS are *repressed by OxyS* expressed constitutively from a multi-copy plasmid or from the chromosome." [Emphasis added] Altuvia *et al.* further points out that "conversely, the two genes are *derepressed in an oxyS deletion strain*. . ." [Emphasis added] (see page 6069, second paragraph of the Introduction).

Applicant submits that Altuvia *et al.* does not teach a system comprising a first and second nucleic acid molecule, wherein the second nucleic acid molecule interacts in *trans* with

the first nucleic acid to *derepress translation of the ORF* as claimed. Furthermore, the teachings of Altuvia *et al.* do not read on a kit comprising a taRNA (*trans-activating* RNA) as claimed. Accordingly, Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Conclusion

Applicant respectfully submits that the present case is in condition for allowance. A Notice to that effect is requested. Applicants would like to thank the Examiner for careful consideration of the present case. If a telephone conversation would help to clarify any issues, or help expedite prosecution of this case, Applicant invites the Examiner to contact the undersigned at (617) 248-4793.

Respectfully submitted,

/Charles E. Lyon/

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